```
=> file caplus medline biosis
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
                                                            0.84       0.84
FULL ESTIMATED COST

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FILE 'BIOSIS' ENTERED AT 09:59:43 ON 13 MAY 2005
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=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
                                                            1.68       2.52
FULL ESTIMATED COST

FILE 'REGISTRY' ENTERED AT 09:59:56 ON 13 MAY 2005
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STRUCTURE FILE UPDATES:   12 MAY 2005  HIGHEST RN 850400-93-0
DICTIONARY FILE UPDATES:  12 MAY 2005  HIGHEST RN 850400-93-0

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TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

  Please note that search-term pricing does apply when
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*************************************************************************
*                                                                       *
* The CA roles and document type information have been removed from     *
* the IDE default display format and the ED field has been added,       *
* effective March 20, 2005.  A new display format, IDERL, is now        *
* available and contains the CA role and document type information.     *
*                                                                       *
*************************************************************************

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> s carbenoxolone/cn
L1             1 CARBENOXOLONE/CN

=> d L1 str cn rn

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2005 ACS on STN

Absolute stereochemistry.
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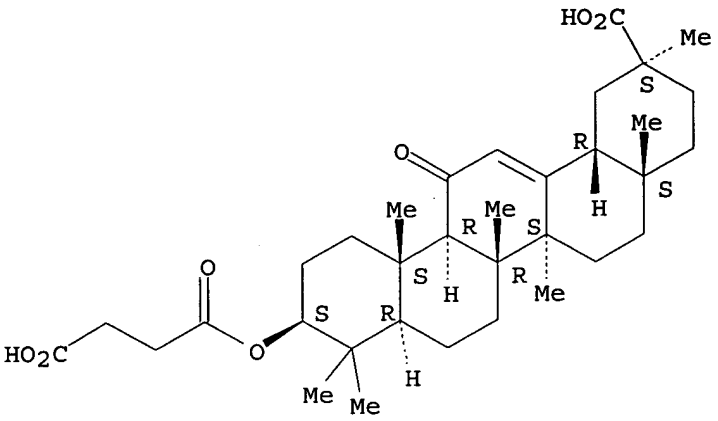

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

CN Olean-12-en-29-oic acid, 3-(3-carboxy-1-oxopropoxy)-11-oxo-, (3β,20β)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Olean-12-en-30-oic acid, 3β-hydroxy-11-oxo-, hydrogen succinate (7CI, 8CI)
CN Olean-12-en-30-oic acid, 3β-hydroxy-11-oxo-, succinate (6CI)
OTHER NAMES:
CN 3-O-(β-Carboxypropionyl)-11-oxo-18β-olean-12-en-30-oic acid
CN 3β-Hydroxy-11-oxoolean-12-en-30-oic acid hydrogen succinate
CN Biogastrone
CN **Carbenoxolone**
CN Glycyrrhetinic acid hydrogen succinate
RN 5697-56-3 REGISTRY

=> file caplus medline biosis

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	7.30	9.82

FILE 'CAPLUS' ENTERED AT 10:01:19 ON 13 MAY 2005
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FILE 'MEDLINE' ENTERED AT 10:01:19 ON 13 MAY 2005

FILE 'BIOSIS' ENTERED AT 10:01:19 ON 13 MAY 2005

=> s 5697-56-3/rn
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L2 328 5697-56-3/RN

=> s obesity or over weight or insulin resistance
L3 204134 OBESITY OR OVER WEIGHT OR INSULIN RESISTANCE

=> s L2 and L3
L4 8 L2 AND L3

=> d 1-8 ibib abs

L4 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:836863 CAPLUS
DOCUMENT NUMBER: 139:333138
TITLE: Pharmaceutical compositions comprising a 11-beta hydroxysteroid dehydrogenase inhibitor and a diuretic agent
INVENTOR(S): Walker, Brian Robert; Seckl, Jonathan Robert
PATENT ASSIGNEE(S): The University of Edinburgh, UK
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003086410	A1	20031023	WO 2003-GB1400	20030331
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1492541	A1	20050105	EP 2003-712434	20030331
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.:

GB 2002-7945	A	20020405
US 2002-375690P	P	20020426
WO 2003-GB1400	W	20030331

AB The authors provide a composition comprising a first agent which is an antagonist of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), together with a second agent comprising a diuretic. The second agent may comprise a mol. which is capable of modulating an interaction between the first agent and 11β-HSD2. Such a composition may be used for improving cognitive ability of an individual, specifically verbal fluency or verbal memory or logical memory (or any combination thereof), or for treatment of Mild Cognitive Impairment (MCI).
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:262481 CAPLUS
DOCUMENT NUMBER: 139:127799
TITLE: Is 11β-hydroxysteroid dehydrogenase type 1 a therapeutic target? Effects of carbenoxolone in lean and obese Zucker rats
AUTHOR(S): Livingstone, Dawn E. W.; Walker, Brian R.
CORPORATE SOURCE: Endocrinology Unit, Department of Medical Sciences, Western General Hospital, University of Edinburgh, Edinburgh, UK
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2003), 305(1), 167-172
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In liver and adipose tissue, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) regenerates glucocorticoids from inactive 11-keto metabolites. Pharmacol. inhibition or transgenic disruption of 11β-HSD1 attenuates glucocorticoid action and increases insulin

sensitivity. Increased adipose 11β-HSD1 may also contribute to the metabolic complications of **obesity.** Here, we examine the effects of inhibition of 11β-HSDs with carbenoxolone in obese insulin-resistant Zucker rats, a strain in which tissue-specific dysregulation of 11β-HSD1 (increased in adipose, decreased in liver) mirrors changes in human **obesity.** Six-week-old male rats were treated orally with carbenoxolone (50 mg/kg/day) or water (1 mL/kg/day) for 3 wk. Carbenoxolone inhibited 11β-HSD1 activity in liver (25±3 vs. 52±2% conversion in lean; 18±3 vs. 35±3% in obese; $p < 0.01$) but not in adipose tissue or skeletal muscle. Carbenoxolone had no effect on weight gain or food intake, did not affect plasma glucose during an oral glucose tolerance test, and increased the plasma insulin response to glucose. However, high-d. lipoprotein cholesterol was increased by carbenoxolone in obese animals (1.52±0.24 vs. 1.21±0.26 mM; $p < 0.03$). Carbenoxolone did not inhibit hepatic inactivation of glucocorticoid by 5β-reductase and had no significant effect on plasma corticosterone levels. In conclusion, carbenoxolone provides a model for liver-specific inhibition of 11β-HSD1, which results in improved lipid profile, in Zucker obese rats. Failure to inhibit 11β-HSD1 in adipose tissue and/or skeletal muscle may explain the lack of effect on glucose tolerance and **obesity.** Inhibition of adipose 11β-HSD1 is probably necessary to gain the maximum benefit of an 11β-HSD1 inhibitor.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:48406 CAPLUS
DOCUMENT NUMBER: 139:17396
TITLE: Effects of the 11β-hydroxysteroid dehydrogenase inhibitor carbenoxolone on insulin sensitivity in men with type 2 diabetes
AUTHOR(S): Andrews, Robert C.; Rooyackers, Olav; Walker, Brian R.
CORPORATE SOURCE: Endocrinology Unit, Department of Medical Sciences, Western General Hospital, University of Edinburgh, Edinburgh, EH4 2XU, UK
SOURCE: Journal of Clinical Endocrinology and Metabolism (2003), 88(1), 285-291
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) regenerates cortisol from inactive cortisone in liver and adipose tissue. Inhibition of 11β-HSD1 offers a novel potential therapy to lower intracellular cortisol concns. and thereby enhance insulin sensitivity and hepatic lipid catabolism in type 2 diabetes, **obesity**, and hyperlipidemia. We evaluated this approach using the nonselective 11β-HSD inhibitor, carbenoxolone, in healthy men and lean male patients with type 2 diabetes. Six diet-controlled nonobese diabetic patients with Hb A1c less than 8%, and six matched controls participated in a double-blind, cross-over comparison of carbenoxolone (100 mg every 8 h, orally, for 7 d) and placebo. They were admitted overnight for infusions of insulin (as required to maintain arterialized plasma glucose of 5.0 mM) and [13C6]glucose. Glucose kinetics were measured in the fasted state from 0700-0730 h, during a 3-h euglycemic hyperinsulinemic clamp (including somatostatin infusion and replacement of physiol. GH and glucagon levels), and during a 2-h euglycemic hyperinsulinemic clamp with a 4-fold increase in glucagon levels. Data are the mean ± SEM. Carbenoxolone had the expected effects of raising blood pressure and lowering plasma potassium. Carbenoxolone reduced total cholesterol in healthy subjects (5.25±0.34 vs. 4.78±0.40 mM; $P < 0.01$), but had no effect on other serum lipids or on cholesterol in diabetic patients. Carbenoxolone did not affect the rate of glucose disposal or the suppression of free fatty acids during hyperinsulinemia. However, carbenoxolone reduced the glucose production rate

during hyperglucagonemia in diabetic patients (1.90±0.2 vs. 1.53±0.3 mg/kg·min; P < 0.05). This was attributable to reduced glycogenolysis (1.31±0.2 vs. 1.01±0.2 mg/kg·min; P < 0.005) rather than altered gluconeogenesis. These observations reinforce the potential metabolic benefits of inhibiting 11β-HSD1 in the liver of patients with type 2 diabetes. Further studies in **obesity** and hyperlipidemia are now warranted. However, clin. useful therapeutic effects will probably require selective 11β-HSD1 inhibitors that lower intraadipose cortisol levels and enhance peripheral glucose uptake.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:754191 CAPLUS
DOCUMENT NUMBER: 137:257667
TITLE: 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1)-lowering agents for lipid profile modulation
INVENTOR(S): Morton, Nicholas Michael; Seckl, Jonathan Robert; Walker, Brian Robert; Andrew, Ruth
PATENT ASSIGNEE(S): The University of Edinburgh, UK
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002076435	A2	20021003	WO 2002-GB1457	20020325
WO 2002076435	A3	20040318		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2441834	AA	20021003	CA 2002-2441834	20020325
GB 2390367	A1	20040107	GB 2003-23962	20020325
GB 2390367	B2	20050413		
EP 1420769	A2	20040526	EP 2002-707001	20020325
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004528308	T2	20040916	JP 2002-574951	20020325
US 2005032761	A1	20050210	US 2003-668564	20030923
PRIORITY APPLN. INFO.:			GB 2001-7383 A	20010323
			WO 2002-GB1457 W	20020325

AB The invention provides use of an agent which lowers levels of 11β-HSD1 in the manufacture of a composition for the promotion of an atheroprotective lipid profile. Agents useful in the invention include e.g. carbenoxolone.

L4 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:307850 CAPLUS
DOCUMENT NUMBER: 133:69071
TITLE: Glucocorticoids, 11β-hydroxysteroid dehydrogenase, and fetal programming
AUTHOR(S): Seckl, Jonathan R.; Cleasby, Mark; Nyirenda, Moffat J.
CORPORATE SOURCE: Molecular Medicine Center, Western General Hospital, University of Edinburgh, Edinburgh, UK

SOURCE: Kidney International (2000), 57(4), 1412-1417
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 74 refs. Epidemiol. studies in many distinct human populations have associated low weight or thinness at birth with a substantially increased risk of cardiovascular and metabolic disorders, including hypertension and **insulin resistance**/type 2 diabetes, in adult life. The concept of fetal "programming" has been advanced to explain this phenomenon. Prenatal glucocorticoid therapy reduces birthweight, and steroids are known to exert long-term organizational effects during specific "windows" of development. Therefore, the authors hypothesized that fetal overexposure to endogenous glucocorticoids might underpin the link between early life events and later disease. In rats, birthweight is reduced following prenatal exposure to the synthetic glucocorticoid dexamethasone, which readily crosses the placenta, or to carbenoxolone, which inhibits 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), the physiol. fetoplacental "barrier" to endogenous glucocorticoids. Although the offspring regain the weight deficit by weaning, as adults they exhibit permanent hypertension, hyperglycemia, and increased hypothalamic-pituitary-adrenal axis activity. Moreover, physiol. variations in placental 11β-HSD2 activity near term correlate directly with fetal weight In humans, 11β-HSD2 gene mutations produce a low birthweight, and some studies show reduced placental 11β-HSD2 activity in association with intrauterine growth retardation. Moreover, low birthweight babies have higher plasma cortisol levels throughout adult life, indicating that hypothalamic-pituitary-adrenal axis programming also occurs in humans. The mol. mechanisms of glucocorticoid programming are beginning to be unraveled and involve permanent and tissue-specific changes in the expression of key genes, notably of the glucocorticoid receptor itself. Thus, glucocorticoid programming may explain, in part, the association between fetal events and subsequent disorders in adult life.

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:156923 CAPLUS
DOCUMENT NUMBER: 132:274485
TITLE: In the search for specific inhibitors of human 11β-hydroxysteroid-dehydrogenases (11β-HSDs): chenodeoxycholic acid selectively inhibits 11β-HSD-I
AUTHOR(S): Diederich, S.; Grossmann, C.; Hanke, B.; Quinkler, M.; Herrmann, M.; Bahr, V.; Oelkers, W.
CORPORATE SOURCE: Department of Endocrinology, Klinikum Benjamin Franklin, Freie Universitat Berlin, Berlin, 12200, Germany
SOURCE: European Journal of Endocrinology (2000), 142(2), 200-207
CODEN: EJOEEP; ISSN: 0804-4643
PUBLISHER: BioScientifica
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: Selective inhibitors of 11β-hydroxysteroid-dehydrogenase type I may be of therapeutical interest for two reasons: (i) 9α-fluorinated 11-dehydrosteroids like 11-dehydro-dexamethasone (DH-D) are rapidly activated by human kidney 11β-hydroxysteroid-dehydrogenase type II (11β-HSD-II) to dexamethasone (D), if the same reaction by hepatic 11β-HSD-I could be selectively inhibited, DH-D could be used for selective renal immunosuppressive therapy; and (ii) reduction of cortisone to cortisol in the liver may increase **insulin resistance** in type 2 diabetes mellitus, and inhibition of the

enzyme may lead to a decrease in gluconeogenesis. Therefore, we characterized the metabolism of DH-D by human hepatic 11β-HSD-I and tried to find a selective inhibitor of this isoenzyme. Methods: For kinetic anal. of 11β-HSD-I, we used microsomes prepared from unaffected parts of liver segments, resected because of hepatocarcinoma or metastatic disease. For inhibition expts., we also tested 11β-HSD-II activity with human kidney cortex microsomes. The inhibitory potency of several compds. was evaluated for oxidation and reduction in concns. from 10-9 to 10-5 mol/L. Results: Whereas D was not oxidized by human liver microsomes at all, cortisol was oxidized to cortisone with a maximum velocity (Vmax) of 95 pmol/mg per min. The reduction of DH-D to D (Vmax = 742 pmol/mg per min, Michaelis-Menten constant (Km) = 1.6 μmol/L) was faster than that of cortisone to cortisol (Vmax = 187 pmol/mg per min). All reactions tested in liver microsomes showed the characteristics of 11β-HSD-I: Km values in the micromolar range, preferred cosubstrate NADP(H), no product inhibition. Of the substances tested for inhibition of 11β-HSD-I and -II, chenodeoxycholic acid was the only one that selectively inhibited 11β-HSD-I (IC50 for reduction: 2.8 + 10-6 mol/L, IC50 for oxidation: 4.4 + 10-6 mol/L), whereas ketoconazole preferentially inhibited oxidation and reduction reactions catalyzed by 11β-HSD-II. Metyrapone, which is reduced to metyrapol by hepatic 11β-HSD-I, inhibited steroid reductase activity of 11β-HSD-I and -II and oxidative activity of 11β-HSD-II. These findings can be explained by substrate competition for reductase reactions and by product inhibition of the oxidation, which is a well-known characteristic of 11β-HSD-II. Conclusions: Our in vitro results may offer a new concept for renal glucocorticoid targeting. Oral administration of small amts. of DH-D (low substrate affinity for 11β-HSD-I) in combination with chenodeoxycholic acid (selective inhibition of 11β-HSD-I) may prevent hepatic first pass reduction of DH-D, thus allowing selective activation of DH-D to D by the high affinity 11β-HSD-II in the kidney. Moreover, selective inhibitors of the hepatic 11β-HSD-I, like chenodeoxycholic acid, may become useful in the therapy of patients with hepatic **insulin resistance** including diabetes mellitus type II, because cortisol enhances gluconeogenesis.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:933168 CAPLUS
DOCUMENT NUMBER: 123:330300
TITLE: Carbenoxolone increases hepatic insulin sensitivity in man: a novel role for 11-oxosteroid reductase in enhancing glucocorticoid receptor activation
AUTHOR(S): Walker, Brian R.; Connacher, Alan A.; Lindsay, R. Mark; Webb, David J.; Edwards, CHristopher R. W.
CORPORATE SOURCE: Department of Medicine, University Edinburgh, Edinburgh, EH4 2XU, UK
SOURCE: Journal of Clinical Endocrinology and Metabolism (1995), 80(11), 3155-9
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the kidney, conversion of cortisol to cortisone by the enzyme 11β-hydroxysteroid dehydrogenase protects mineralocorticoid receptors from cortisol. In the liver, a different isoform of the enzyme favors 11β-reductase conversion of cortisone to cortisol. The authors have tested the hypothesis that hepatic 11β-reductase enhances glucocorticoid receptor activation in the liver by inhibiting the enzyme with carbenoxolone and observing effects on insulin sensitivity. Seven healthy males took part in a double blind randomized cross-over study in which oral carbenoxolone (100 mg every 8 h) or placebo was administered for 7 days. Euglycemic hyperinsulinemic clamp studies were then performed, including measurement of forearm glucose uptake. Carbenoxolone

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

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*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*
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Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

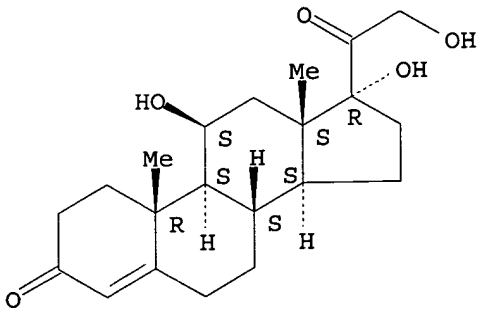
=> s carticosol/cn
L7 0 CARTICOSOL/CN

=> s cortisol/cn
L8 1 CORTISOL/CN

=> d L8 str cn rn

L8 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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OTHER CA INDEX NAMES:
CN **Cortisol (8CI)**
OTHER NAMES:
CN 11β,17,21-Trihydroxypregn-4-ene-3,20-dione
CN 11β,17,21-Trihydroxyprogesterone
CN 11β,17α,21-Trihydroxypregn-4-ene-3,20-dione
CN 11β-Hydroxycortisone
CN 17-Hydroxycorticosterone
CN 17α-Hydroxycorticosterone
CN 28: PN: US20030109453 SEQID: 27 claimed sequence
CN 4-Pregnene-11β,17α,21-triol-3,20-dione
CN Acticort
CN Aeroseb HC
CN Ala-Cort

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CN   Anflam
CN   Anti-inflammatory hormone
CN   CaldeCort Spray
CN   CCN 90306A
CN   Cetacort
CN   Cobadex
CN   Cort-Dome
CN   Cortanal
CN   Cortef
CN   Cortenema
CN   Corticreme
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CN   Cortiment
CN   Cortispray
CN   Cortonema
CN   Cortril
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CN   Dermocortal
CN   Dermolate
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CN   Dioderm
CN   Domolene-HC
CN   Efcorbin
CN   Efcortelan
CN   Eldecort
CN   Epiderm H
CN   Esiderm H
CN   Evacort
CN   Ficortril
CN   Genacort
CN   HC
CN   Heb-Cort
CN   Hidro-Colisona
CN   Hycort
CN   Hycortol
CN   Hycortole
CN   Hydracort
CN   Hydrasson
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for
     DISPLAY
RN   50-23-7  REGISTRY


=> d hist

     (FILE 'HOME' ENTERED AT 09:57:20 ON 13 MAY 2005)

     FILE 'CAPLUS, MEDLINE, BIOSIS' ENTERED AT 09:59:43 ON 13 MAY 2005

     FILE 'REGISTRY' ENTERED AT 09:59:56 ON 13 MAY 2005
L1             1 S CARBENOXOLONE/CN

     FILE 'CAPLUS, MEDLINE, BIOSIS' ENTERED AT 10:01:19 ON 13 MAY 2005
L2           328 S 5697-56-3/RN
L3        204134 S OBESITY OR OVER WEIGHT OR INSULIN RESISTANCE
L4             8 S L2 AND L3
                 E WALKER/AU
L5            92 S E9
                 E WALKER B/AU
                 E WALKER B R/AU
L6           475 S E3

     FILE 'REGISTRY' ENTERED AT 10:19:10 ON 13 MAY 2005
L7             0 S CARTICOSOL/CN
L8             1 S CORTISOL/CN
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=> file caplus medline embase biosis
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                        12.33      79.48

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                           ENTRY    SESSION
CA SUBSCRIBER PRICE                                         0.00      -5.84

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FILE 'BIOSIS' ENTERED AT 10:20:49 ON 13 MAY 2005
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=> s 50-23-7/RN
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L9       35775 50-23-7/RN

=> s L1 and L9
L10          35 L1 AND L9

=> s L10 and L3
L11           4 L10 AND L3

=> d 1-4 ibib abs

L11  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2003:48406  CAPLUS
DOCUMENT NUMBER:          139:17396
TITLE:                    Effects of the 11β-hydroxysteroid dehydrogenase
                          inhibitor carbenoxolone on insulin sensitivity in men
                          with type 2 diabetes
AUTHOR(S):                Andrews, Robert C.; Rooyackers, Olav; Walker, Brian R.
CORPORATE SOURCE:         Endocrinology Unit, Department of Medical Sciences,
                          Western General Hospital, University of Edinburgh,
                          Edinburgh, EH4 2XU, UK
SOURCE:                   Journal of Clinical Endocrinology and Metabolism
                          (2003), 88(1), 285-291
                          CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER:                Endocrine Society
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) regenerates
     cortisol from inactive cortisone in liver and adipose tissue.  Inhibition
     of 11β-HSD1 offers a novel potential therapy to lower intracellular
     cortisol concns. and thereby enhance insulin sensitivity and hepatic lipid
     catabolism in type 2 diabetes, obesity, and hyperlipidemia.  We
     evaluated this approach using the nonselective 11β-HSD inhibitor,
     carbenoxolone, in healthy men and lean male patients with type 2 diabetes.
     Six diet-controlled nonobese diabetic patients with Hb A1c less than 8%,
     and six matched controls participated in a double-blind, cross-over
     comparison of carbenoxolone (100 mg every 8 h, orally, for 7 d) and
     placebo.  They were admitted overnight for infusions of insulin (as
     required to maintain arterialized plasma glucose of 5.0 mM) and
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[13C6]glucose. Glucose kinetics were measured in the fasted state from 0700-0730 h, during a 3-h euglycemic hyperinsulinemic clamp (including somatostatin infusion and replacement of physiol. GH and glucagon levels), and during a 2-h euglycemic hyperinsulinemic clamp with a 4-fold increase in glucagon levels. Data are the mean ± SEM. Carbenoxolone had the expected effects of raising blood pressure and lowering plasma potassium. Carbenoxolone reduced total cholesterol in healthy subjects (5.25±0.34 vs. 4.78±0.40 mM; P < 0.01), but had no effect on other serum lipids or on cholesterol in diabetic patients. Carbenoxolone did not affect the rate of glucose disposal or the suppression of free fatty acids during hyperinsulinemia. However, carbenoxolone reduced the glucose production rate during hyperglucagonemia in diabetic patients (1.90±0.2 vs. 1.53±0.3 mg/kg·min; P < 0.05). This was attributable to reduced glycogenolysis (1.31±0.2 vs. 1.01±0.2 mg/kg·min; P < 0.005) rather than altered gluconeogenesis. These observations reinforce the potential metabolic benefits of inhibiting 11β-HSD1 in the liver of patients with type 2 diabetes. Further studies in **obesity** and hyperlipidemia are now warranted. However, clin. useful therapeutic effects will probably require selective 11β-HSD1 inhibitors that lower intraadipose cortisol levels and enhance peripheral glucose uptake.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:754191 CAPLUS

DOCUMENT NUMBER: 137:257667

TITLE: 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1)-lowering agents for lipid profile modulation

INVENTOR(S): Morton, Nicholas Michael; Seckl, Jonathan Robert; Walker, Brian Robert; Andrew, Ruth

PATENT ASSIGNEE(S): The University of Edinburgh, UK

SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002076435	A2	20021003	WO 2002-GB1457		20020325
WO 2002076435	A3	20040318			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2441834	AA	20021003	CA 2002-2441834		20020325
GB 2390367	A1	20040107	GB 2003-23962		20020325
GB 2390367	B2	20050413			
EP 1420769	A2	20040526	EP 2002-707001		20020325
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004528308	T2	20040916	JP 2002-574951		20020325
US 2005032761	A1	20050210	US 2003-668564		20030923
PRIORITY APPLN. INFO.:			GB 2001-7383	A	20010323
			WO 2002-GB1457	W	20020325

AB The invention provides use of an agent which lowers levels of 11β-HSD1 in the manufacture of a composition for the promotion of an

atheroprotective lipid profile. Agents useful in the invention include e.g. carbenoxolone.

L11 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:307850 CAPLUS
DOCUMENT NUMBER: 133:69071
TITLE: Glucocorticoids, 11β-hydroxysteroid dehydrogenase, and fetal programming
AUTHOR(S): Seckl, Jonathan R.; Cleasby, Mark; Nyirenda, Moffat J.
CORPORATE SOURCE: Molecular Medicine Center, Western General Hospital, University of Edinburgh, Edinburgh, UK
SOURCE: Kidney International (2000), 57(4), 1412-1417
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 74 refs. Epidemiol. studies in many distinct human populations have associated low weight or thinness at birth with a substantially increased risk of cardiovascular and metabolic disorders, including hypertension and **insulin resistance**/type 2 diabetes, in adult life. The concept of fetal "programming" has been advanced to explain this phenomenon. Prenatal glucocorticoid therapy reduces birthweight, and steroids are known to exert long-term organizational effects during specific "windows" of development. Therefore, the authors hypothesized that fetal overexposure to endogenous glucocorticoids might underpin the link between early life events and later disease. In rats, birthweight is reduced following prenatal exposure to the synthetic glucocorticoid dexamethasone, which readily crosses the placenta, or to carbenoxolone, which inhibits 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), the physiol. fetoplacental "barrier" to endogenous glucocorticoids. Although the offspring regain the weight deficit by weaning, as adults they exhibit permanent hypertension, hyperglycemia, and increased hypothalamic-pituitary-adrenal axis activity. Moreover, physiol. variations in placental 11β-HSD2 activity near term correlate directly with fetal weight In humans, 11β-HSD2 gene mutations produce a low birthweight, and some studies show reduced placental 11β-HSD2 activity in association with intrauterine growth retardation. Moreover, low birthweight babies have higher plasma cortisol levels throughout adult life, indicating that hypothalamic-pituitary-adrenal axis programming also occurs in humans. The mol. mechanisms of glucocorticoid programming are beginning to be unraveled and involve permanent and tissue-specific changes in the expression of key genes, notably of the glucocorticoid receptor itself. Thus, glucocorticoid programming may explain, in part, the association between fetal events and subsequent disorders in adult life.
REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:156923 CAPLUS
DOCUMENT NUMBER: 132:274485
TITLE: In the search for specific inhibitors of human 11β-hydroxysteroid-dehydrogenases (11β-HSDs): chenodeoxycholic acid selectively inhibits 11β-HSD-I
AUTHOR(S): Diederich, S.; Grossmann, C.; Hanke, B.; Quinkler, M.; Herrmann, M.; Bahr, V.; Oelkers, W.
CORPORATE SOURCE: Department of Endocrinology, Klinikum Benjamin Franklin, Freie Universitat Berlin, Berlin, 12200, Germany
SOURCE: European Journal of Endocrinology (2000), 142(2), 200-207
CODEN: EJOEEP; ISSN: 0804-4643
PUBLISHER: BioScientifica

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: Selective inhibitors of 11β-hydroxysteroid-dehydrogenase type I may be of therapeutical interest for two reasons: (i) 9α-fluorinated 11-dehydrosteroids like 11-dehydro-dexamethasone (DH-D) are rapidly activated by human kidney 11β-hydroxysteroid-dehydrogenase type II (11β-HSD-II) to dexamethasone (D), if the same reaction by hepatic 11β-HSD-I could be selectively inhibited, DH-D could be used for selective renal immunosuppressive therapy; and (ii) reduction of cortisone to cortisol in the liver may increase **insulin resistance** in type 2 diabetes mellitus, and inhibition of the enzyme may lead to a decrease in gluconeogenesis. Therefore, we characterized the metabolism of DH-D by human hepatic 11β-HSD-I and tried to find a selective inhibitor of this isoenzyme. Methods: For kinetic anal. of 11β-HSD-I, we used microsomes prepared from unaffected parts of liver segments, resected because of hepatocarcinoma or metastatic disease. For inhibition expts., we also tested 11β-HSD-II activity with human kidney cortex microsomes. The inhibitory potency of several compds. was evaluated for oxidation and reduction in concns. from 10-9 to 10-5 mol/L. Results: Whereas D was not oxidized by human liver microsomes at all, cortisol was oxidized to cortisone with a maximum velocity (Vmax) of 95 pmol/mg per min. The reduction of DH-D to D (Vmax = 742 pmol/mg per min, Michaelis-Menten constant (Km) = 1.6 μmol/L) was faster than that of cortisone to cortisol (Vmax = 187 pmol/mg per min). All reactions tested in liver microsomes showed the characteristics of 11β-HSD-I: Km values in the micromolar range, preferred cosubstrate NADP(H), no product inhibition. Of the substances tested for inhibition of 11β-HSD-I and -II, chenodeoxycholic acid was the only one that selectively inhibited 11β-HSD-I (IC50 for reduction: 2.8 + 10-6 mol/L, IC50 for oxidation: 4.4 + 10-6 mol/L), whereas ketoconazole preferentially inhibited oxidation and reduction reactions catalyzed by 11β-HSD-II. Metyrapone, which is reduced to metyrapol by hepatic 11β-HSD-I, inhibited steroid reductase activity of 11β-HSD-I and -II and oxidative activity of 11β-HSD-II. These findings can be explained by substrate competition for reductase reactions and by product inhibition of the oxidation, which is a well-known characteristic of 11β-HSD-II. Conclusions: Our in vitro results may offer a new concept for renal glucocorticoid targeting. Oral administration of small amts. of DH-D (low substrate affinity for 11β-HSD-I) in combination with chenodeoxycholic acid (selective inhibition of 11β-HSD-I) may prevent hepatic first pass reduction of DH-D, thus allowing selective activation of DH-D to D by the high affinity 11β-HSD-II in the kidney. Moreover, selective inhibitors of the hepatic 11β-HSD-I, like chenodeoxycholic acid, may become useful in the therapy of patients with hepatic **insulin resistance** including diabetes mellitus type II, because cortisol enhances gluconeogenesis.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s beta-hydroxysteroid dehydrogenase
L12 19232 BETA-HYDROXYSTEROID DEHYDROGENASE

=> s L2 and L9
'RN' IS NOT A VALID FIELD CODE
L13 35 L2 AND L9

=> s L2 and L12
'RN' IS NOT A VALID FIELD CODE
L14 62 L2 AND L12

=> s L14 and L3
L15 7 L14 AND L3

=> d 1-7 ibib abs

L15 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:836863 CAPLUS
DOCUMENT NUMBER: 139:333138
TITLE: Pharmaceutical compositions comprising a 11-**beta hydroxysteroid dehydrogenase** inhibitor and a diuretic agent
INVENTOR(S): Walker, Brian Robert; Seckl, Jonathan Robert
PATENT ASSIGNEE(S): The University of Edinburgh, UK
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003086410	A1	20031023	WO 2003-GB1400	20030331
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1492541	A1	20050105	EP 2003-712434	20030331
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.:

GB 2002-7945	A	20020405
US 2002-375690P	P	20020426
WO 2003-GB1400	W	20030331

AB The authors provide a composition comprising a first agent which is an antagonist of 11β -**hydroxysteroid dehydrogenase** type 1 (11β-HSD1), together with a second agent comprising a diuretic. The second agent may comprise a mol. which is capable of modulating an interaction between the first agent and 11β-HSD2. Such a composition may be used for improving cognitive ability of an individual, specifically verbal fluency or verbal memory or logical memory (or any combination thereof), or for treatment of Mild Cognitive Impairment (MCI).
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:262481 CAPLUS
DOCUMENT NUMBER: 139:127799
TITLE: Is 11β -**hydroxysteroid dehydrogenase** type 1 a therapeutic target? Effects of carbenoxolone in lean and obese Zucker rats
AUTHOR(S): Livingstone, Dawn E. W.; Walker, Brian R.
CORPORATE SOURCE: Endocrinology Unit, Department of Medical Sciences, Western General Hospital, University of Edinburgh, Edinburgh, UK
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2003), 305(1), 167-172
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In liver and adipose tissue, 11β -**hydroxysteroid**

dehydrogenase type 1 (11β-HSD1) regenerates glucocorticoids from inactive 11-keto metabolites. Pharmacol. inhibition or transgenic disruption of 11β-HSD1 attenuates glucocorticoid action and increases insulin sensitivity. Increased adipose 11β-HSD1 may also contribute to the metabolic complications of **obesity.** Here, we examine the effects of inhibition of 11β-HSDs with carbenoxolone in obese insulin-resistant Zucker rats, a strain in which tissue-specific dysregulation of 11β-HSD1 (increased in adipose, decreased in liver) mirrors changes in human **obesity.** Six-week-old male rats were treated orally with carbenoxolone (50 mg/kg/day) or water (1 mL/kg/day) for 3 wk. Carbenoxolone inhibited 11β-HSD1 activity in liver (25±3 vs. 52±2% conversion in lean; 18±3 vs. 35±3% in obese; $p < 0.01$) but not in adipose tissue or skeletal muscle. Carbenoxolone had no effect on weight gain or food intake, did not affect plasma glucose during an oral glucose tolerance test, and increased the plasma insulin response to glucose. However, high-d. lipoprotein cholesterol was increased by carbenoxolone in obese animals (1.52±0.24 vs. 1.21±0.26 mM; $p < 0.03$). Carbenoxolone did not inhibit hepatic inactivation of glucocorticoid by 5β-reductase and had no significant effect on plasma corticosterone levels. In conclusion, carbenoxolone provides a model for liver-specific inhibition of 11β-HSD1, which results in improved lipid profile, in Zucker obese rats. Failure to inhibit 11β-HSD1 in adipose tissue and/or skeletal muscle may explain the lack of effect on glucose tolerance and **obesity.** Inhibition of adipose 11β-HSD1 is probably necessary to gain the maximum benefit of an 11β-HSD1 inhibitor.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:48406 CAPLUS
DOCUMENT NUMBER: 139:17396
TITLE: Effects of the 11β -**hydroxysteroid dehydrogenase** inhibitor carbenoxolone on insulin sensitivity in men with type 2 diabetes
AUTHOR(S): Andrews, Robert C.; Rooyackers, Olav; Walker, Brian R.
CORPORATE SOURCE: Endocrinology Unit, Department of Medical Sciences, Western General Hospital, University of Edinburgh, Edinburgh, EH4 2XU, UK
SOURCE: Journal of Clinical Endocrinology and Metabolism (2003), 88(1), 285-291
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 11β -**Hydroxysteroid dehydrogenase** type 1 (11β-HSD1) regenerates cortisol from inactive cortisone in liver and adipose tissue. Inhibition of 11β-HSD1 offers a novel potential therapy to lower intracellular cortisol concns. and thereby enhance insulin sensitivity and hepatic lipid catabolism in type 2 diabetes, **obesity**, and hyperlipidemia. We evaluated this approach using the nonselective 11β-HSD inhibitor, carbenoxolone, in healthy men and lean male patients with type 2 diabetes. Six diet-controlled nonobese diabetic patients with Hb A1c less than 8%, and six matched controls participated in a double-blind, cross-over comparison of carbenoxolone (100 mg every 8 h, orally, for 7 d) and placebo. They were admitted overnight for infusions of insulin (as required to maintain arterialized plasma glucose of 5.0 mM) and [13C6]glucose. Glucose kinetics were measured in the fasted state from 0700-0730 h, during a 3-h euglycemic hyperinsulinemic clamp (including somatostatin infusion and replacement of physiol. GH and glucagon levels), and during a 2-h euglycemic hyperinsulinemic clamp with a 4-fold increase in glucagon levels. Data are the mean ± SEM. Carbenoxolone had the expected effects of raising blood pressure and lowering plasma potassium. Carbenoxolone reduced total

cholesterol in healthy subjects (5.25±0.34 vs. 4.78±0.40 mM; P < 0.01), but had no effect on other serum lipids or on cholesterol in diabetic patients. Carbenoxolone did not affect the rate of glucose disposal or the suppression of free fatty acids during hyperinsulinemia. However, carbenoxolone reduced the glucose production rate during hyperglucagonemia in diabetic patients (1.90±0.2 vs. 1.53±0.3 mg/kg·min; P < 0.05). This was attributable to reduced glycogenolysis (1.31±0.2 vs. 1.01±0.2 mg/kg·min; P < 0.005) rather than altered gluconeogenesis. These observations reinforce the potential metabolic benefits of inhibiting 11β-HSD1 in the liver of patients with type 2 diabetes. Further studies in **obesity** and hyperlipidemia are now warranted. However, clin. useful therapeutic effects will probably require selective 11β-HSD1 inhibitors that lower intraadipose cortisol levels and enhance peripheral glucose uptake.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:754191 CAPLUS
DOCUMENT NUMBER: 137:257667
TITLE: 11β -**Hydroxysteroid dehydrogenase** type 1 (11β-HSD1)-lowering agents for lipid profile modulation
INVENTOR(S): Morton, Nicholas Michael; Seckl, Jonathan Robert; Walker, Brian Robert; Andrew, Ruth
PATENT ASSIGNEE(S): The University of Edinburgh, UK
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002076435	A2	20021003	WO 2002-GB1457	20020325
WO 2002076435	A3	20040318		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2441834	AA	20021003	CA 2002-2441834	20020325
GB 2390367	A1	20040107	GB 2003-23962	20020325
GB 2390367	B2	20050413		
EP 1420769	A2	20040526	EP 2002-707001	20020325
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004528308	T2	20040916	JP 2002-574951	20020325
US 2005032761	A1	20050210	US 2003-668564	20030923
PRIORITY APPLN. INFO.:			GB 2001-7383 A	20010323
			WO 2002-GB1457 W	20020325

AB The invention provides use of an agent which lowers levels of 11β-HSD1 in the manufacture of a composition for the promotion of an atheroprotective lipid profile. Agents useful in the invention include e.g. carbenoxolone.

L15 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:307850 CAPLUS
DOCUMENT NUMBER: 133:69071

TITLE: Glucocorticoids, 11β - **hydroxysteroid dehydrogenase**, and fetal programming
AUTHOR(S): Seckl, Jonathan R.; Cleasby, Mark; Nyirenda, Moffat J.
CORPORATE SOURCE: Molecular Medicine Center, Western General Hospital, University of Edinburgh, Edinburgh, UK
SOURCE: Kidney International (2000), 57(4), 1412-1417
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 74 refs. Epidemiol. studies in many distinct human populations have associated low weight or thinness at birth with a substantially increased risk of cardiovascular and metabolic disorders, including hypertension and **insulin resistance**/type 2 diabetes, in adult life. The concept of fetal "programming" has been advanced to explain this phenomenon. Prenatal glucocorticoid therapy reduces birthweight, and steroids are known to exert long-term organizational effects during specific "windows" of development. Therefore, the authors hypothesized that fetal overexposure to endogenous glucocorticoids might underpin the link between early life events and later disease. In rats, birthweight is reduced following prenatal exposure to the synthetic glucocorticoid dexamethasone, which readily crosses the placenta, or to carbenoxolone, which inhibits 11β -**hydroxysteroid dehydrogenase** type 2 (11β-HSD2), the physiol. fetoplacental "barrier" to endogenous glucocorticoids. Although the offspring regain the weight deficit by weaning, as adults they exhibit permanent hypertension, hyperglycemia, and increased hypothalamic-pituitary-adrenal axis activity. Moreover, physiol. variations in placental 11β-HSD2 activity near term correlate directly with fetal weight In humans, 11β-HSD2 gene mutations produce a low birthweight, and some studies show reduced placental 11β-HSD2 activity in association with intrauterine growth retardation. Moreover, low birthweight babies have higher plasma cortisol levels throughout adult life, indicating that hypothalamic-pituitary-adrenal axis programming also occurs in humans. The mol. mechanisms of glucocorticoid programming are beginning to be unraveled and involve permanent and tissue-specific changes in the expression of key genes, notably of the glucocorticoid receptor itself. Thus, glucocorticoid programming may explain, in part, the association between fetal events and subsequent disorders in adult life.
REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:156923 CAPLUS
DOCUMENT NUMBER: 132:274485
TITLE: In the search for specific inhibitors of human 11. **beta.-hydroxysteroid-dehydrogenases** (11β-HSDs): chenodeoxycholic acid selectively inhibits 11β-HSD-I
AUTHOR(S): Diederich, S.; Grossmann, C.; Hanke, B.; Quinkler, M.; Herrmann, M.; Bahr, V.; Oelkers, W.
CORPORATE SOURCE: Department of Endocrinology, Klinikum Benjamin Franklin, Freie Universitat Berlin, Berlin, 12200, Germany
SOURCE: European Journal of Endocrinology (2000), 142(2), 200-207
CODEN: EJOEEP; ISSN: 0804-4643
PUBLISHER: BioScientifica
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: Selective inhibitors of 11β - **hydroxysteroid-dehydrogenase** type I may be of

therapeutical interest for two reasons: (i) 9α-fluorinated 11-dehydrosteroids like 11-dehydro-dexamethasone (DH-D) are rapidly activated by human kidney 11β -**hydroxysteroid-dehydrogenase** type II (11β-HSD-II) to dexamethasone (D), if the same reaction by hepatic 11β-HSD-I could be selectively inhibited, DH-D could be used for selective renal immunosuppressive therapy; and (ii) reduction of cortisone to cortisol in the liver may increase **insulin resistance** in type 2 diabetes mellitus, and inhibition of the enzyme may lead to a decrease in gluconeogenesis. Therefore, we characterized the metabolism of DH-D by human hepatic 11β-HSD-I and tried to find a selective inhibitor of this isoenzyme. Methods: For kinetic anal. of 11β-HSD-I, we used microsomes prepared from unaffected parts of liver segments, resected because of hepatocarcinoma or metastatic disease. For inhibition expts., we also tested 11β-HSD-II activity with human kidney cortex microsomes. The inhibitory potency of several compds. was evaluated for oxidation and reduction in concns. from 10-9 to 10-5 mol/L. Results: Whereas D was not oxidized by human liver microsomes at all, cortisol was oxidized to cortisone with a maximum velocity (Vmax) of 95 pmol/mg per min. The reduction of DH-D to D (Vmax = 742 pmol/mg per min, Michaelis-Menten constant (Km) = 1.6 μmol/L) was faster than that of cortisone to cortisol (Vmax = 187 pmol/mg per min). All reactions tested in liver microsomes showed the characteristics of 11β-HSD-I: Km values in the micromolar range, preferred cosubstrate NADP(H), no product inhibition. Of the substances tested for inhibition of 11β-HSD-I and -II, chenodeoxycholic acid was the only one that selectively inhibited 11β-HSD-I (IC50 for reduction: 2.8 + 10-6 mol/L, IC50 for oxidation: 4.4 + 10-6 mol/L), whereas ketoconazole preferentially inhibited oxidation and reduction reactions catalyzed by 11β-HSD-II. Metyrapone, which is reduced to metyrapol by hepatic 11β-HSD-I, inhibited steroid reductase activity of 11β-HSD-I and -II and oxidative activity of 11β-HSD-II. These findings can be explained by substrate competition for reductase reactions and by product inhibition of the oxidation, which is a well-known characteristic of 11β-HSD-II. Conclusions: Our in vitro results may offer a new concept for renal glucocorticoid targeting. Oral administration of small amts. of DH-D (low substrate affinity for 11β-HSD-I) in combination with chenodeoxycholic acid (selective inhibition of 11β-HSD-I) may prevent hepatic first pass reduction of DH-D, thus allowing selective activation of DH-D to D by the high affinity 11β-HSD-II in the kidney. Moreover, selective inhibitors of the hepatic 11β-HSD-I, like chenodeoxycholic acid, may become useful in the therapy of patients with hepatic **insulin resistance** including diabetes mellitus type II, because cortisol enhances gluconeogenesis.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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TITLE: Carbenoxolone increases hepatic insulin sensitivity in man: a novel role for 11-oxosteroid reductase in enhancing glucocorticoid receptor activation

AUTHOR(S): Walker, Brian R.; Connacher, Alan A.; Lindsay, R. Mark; Webb, David J.; Edwards, CHristopher R. W.

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AB In the kidney, conversion of cortisol to cortisone by the enzyme 11. **beta.-hydroxysteroid dehydrogenase** protects mineralocorticoid receptors from cortisol. In the liver, a different

isoform of the enzyme favors 11β-reductase conversion of cortisone to cortisol. The authors have tested the hypothesis that hepatic 11β-reductase enhances glucocorticoid receptor activation in the liver by inhibiting the enzyme with carbenoxolone and observing effects on insulin sensitivity. Seven healthy males took part in a double blind randomized cross-over study in which oral carbenoxolone (100 mg every 8 h) or placebo was administered for 7 days. Euglycemic hyperinsulinemic clamp studies were then performed, including measurement of forearm glucose uptake. Carbenoxolone increased whole body insulin sensitivity (M values for dextrose infusion rates, 41.1 μmol/kg.min for placebo vs. 44.6 for carbenoxolone), but had no effect on forearm insulin sensitivity. The authors infer that carbenoxolone, by inhibiting hepatic 11β-reductase and reducing intrahepatic cortisol concentration, increases hepatic insulin sensitivity and decreases glucose production Thus, plasma cortisone provides an inactive pool that can be converted to active glucocorticoids at sites where 11β-reductase is expressed, abnormal hepatic 11β-reductase activity might be important in syndromes of **insulin resistance**, and manipulation of hepatic 11β-reductase may be useful in treating **insulin resistance.**

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